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Catalytic Hydrogenation of Carboxylic Acid Esters, Amides, and Nitriles with Homogeneous Catalysts

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ABSTRACT: This review describes the catalytic reduction of amides, carboxylic acid esters and nitriles with homogeneous catalysts using molecular hydrogen as an environmental friendly reducing agent.

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1. INTRODUCTION

Traditionally, the reduction of substituted carboxylic acid derivatives such as amides, esters, and nitriles has been performed using stoichiometric amounts of metal hydride reagents. Unfortunately, these methods produce a considerable amount of waste and are inherently unsafe. Obviously, catalytic reactions using molecular hydrogen are more attractive since H_2 is preferred as a reducing agent due to its environmental friendliness and price. So far, mainly heterogeneous catalysts are known to promote such hydrogenations under harsh conditions. In contrast, homogeneous, molecular-defined organometallic complexes are often considered to be more active at lower reaction temperatures and hydrogen pressures, which might lead to higher selectivity. Hence, in recent years enormous progress has been achieved in the area of nitrile hydrogenation to amines, which are high-value intermediates in the bulk- and fine chemicals industry, e.g. plastics, surfactants, textiles, dyes, drugs, and papers. Similar improvements were realized for the selective reduction of esters towards the corresponding alcohols. The resulting products represent useful building blocks for the chemical, pharmaceutical, and agrochemical industries as well as the flavor and fragrance industry. Here, we present a critical overview of the recent developments in catalytic hydrogenations of amides, nitriles, and esters using organometallic catalysts. Moreover, we highlight the most interesting and important applications.

2. CATALYTIC REDUCTION OF AMIDES

Amides are known to be thermodynamically highly stable carboxylic acid derivatives, which are easily accessible from the corresponding acid or via aminocarbonylation from olefins or aryl-X derivatives.[1] Combining these latter methods with a subsequent catalytic hydrogenation step represents an attractive overall process to create selectively aliphatic or benzylic C–N bonds. Unfortunately, as shown in Scheme 1, the hydrogenation of amides can lead to either the preferred amine or the in general "undesired" alcohol.

In the first reduction step, the corresponding hemiaminal is formed by a formal addition of molecular hydrogen to the carbonyl group of the amide. This hemiaminal is in equilibrium with the imine (via dehydration) or the corresponding aldehyde, depending on the reaction conditions. Subsequently, catalytic hydrogenation of the imine (A) or the aldehyde (B) leads to the amine or alcohol, respectively. It should also be noted that the direct hydrogenolysis of hemiaminal derivatives has been proposed.[2]

2.1. C–N cleavage. In 2003, the first example of a homogeneously catalyzed hydrogenation of amides has been described.[3] In their work, Crabtree and co-workers observed the reduction of propanamide at high temperature (160 °C). More specifically, a mixture of products including the secondary amine, propanol, alkylated amide, and ester were obtained using $Ru(acac)_3$ in combination with the so-called $Triphos^{Ph}$ ligand (1,1,1-tris(diphenylphosphinomethyl)ethane) (Scheme 2).

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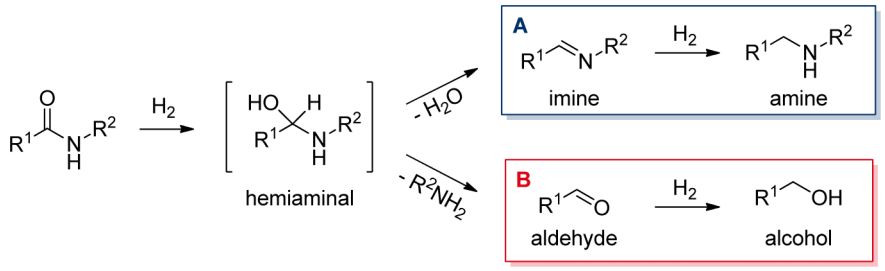
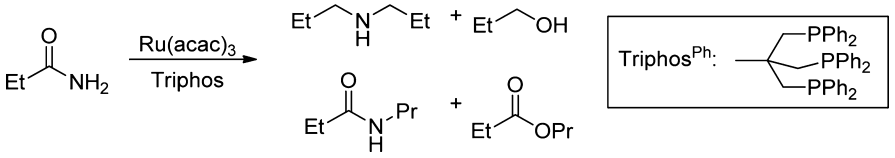
Scheme 1. Two possible reaction pathways for the hydrogenation of amides



Scheme 2. First example of a homogeneous amide hydrogenation by Crabtree et al.



Progress on this and related reactions was reported by the group of Ikariya starting in 2006. They used various ruthenium complexes, e.g. [Cp*RuCl(*PN*)] and [Cp*RuCl(*LN*)] (Cp* = η-$C_5(CH_3)_5$, *PN* = $Ph_2P(CH_2)_2NH_2$, *LN* = 2-$C_5H_4NCH_2NH_2$), for the hydrogenation of cyclic imides,[4a,d] acylcarbamates, as well as acylsulfonamides,[4b] lactams, and amides.[4c,e] As a drawback the reductive cleavage of the C−N bond needed reaction times up to 72 h in the presence of up to 2.5 equiv of base and hydrogen pressure between 30 and 50 bar. Remarkably, in case of imides the group of Ikariya established hydrogenative ring-openings of unsymmetrical substrates in a regioselective manner[4a] and enantioselective desymmetrizations of bicyclic imides with a prochiral center.[4d] Furthermore, they reported in 2011 the first example of a direct hydrogenative kinetic resolution of a racemic lactone to give an optically active diol. However, the observed enantioselectivities were only moderate between 11 and 32% ee.

More recently, a breakthrough on amide hydrogenation was presented by Milstein and co-workers using ruthenium pincer complexes with so-called non-innocent ligands.[5] On the basis of their previous study of aromatization−dearomatization of pyridine[6] and acridine-derived[7] pincer ligands, they applied dearomatized bipyridyl pincer ligands under milder conditions (Figure 1).[8]

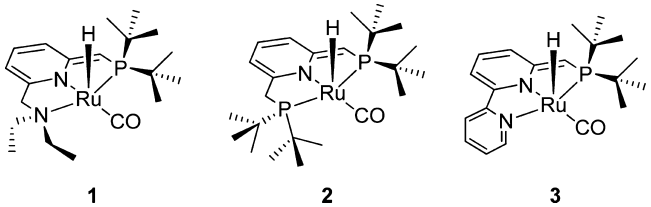


Figure 1. Dearomatized Ru-pincer complexes.

As shown in Scheme 3, the application of complex **3** gave best results with a number of representative substrates, whereby no functional group tolerance, e.g. halides, nitro, amino, or amide groups, was presented in this latter case. In contrast to previous works by Crabtree or Ikariya low pressure, neutral milieu, and no additives were necessary to form the desired amines directly by avoiding side reactions, e.g. hydrolytic cleavage.

Shortly after this work, complex **3** was applied for the catalytic reduction of related urea derivatives to give the corresponding amines and methanol.[9] Again, the reduction proceeded under mild and neutral reaction conditions. According to the authors, this protocol represented the first catalytic hydrogenation of ureas with homogeneous catalysts.

Around the same time, Bergens et al. described the reduction of secondary and tertiary amides as well as lactams without the help of strongly activating functional groups.[10] Using the π-allyl ruthenium complex **4** (Figure 2) the hydrogenation of several lactams occurred in quantitative yield and with catalyst TONs up to 1000. Similar good results were obtained for acyclic amides (Scheme 4).

Remarkably, complexes **4** and $[Ru(Cl)_2(Ph_2P(CH_2)_2NH_2)_2]$ (**5**) shown in Figure 2, which were also used by Saudan[11] for active ester hydrogenation (see section 3.1), led to high TONs of 7120 (complex **4**) and 6760 (complex **5**) for the hydrogenation of *N*-phenylpyrrolidin-2-one, respectively.

2.2. C−O cleavage. The more interesting hydrogenation with C−O cleavage was successfully realized by Cole-Hamilton and co-workers using primary and secondary amides[12] on the basis of Crabtree's original development. $Ru(acac)_3$ in combination with Triphos^{Ph} and molecular hydrogen reduced *N*-phenylnonamide at comparably high temperature (164 °C) as shown in Scheme 5. Notably, the addition of water was necessary to stabilize the active catalyst.

It is worthwhile to mention that in their protocol also nonanoic acid was hydrogenated under an ammonia atmosphere, leading to a mixture of primary amine (15%), secondary amine (47%), alcohol (3%), and secondary amide (35%). In addition, a suitable mechanism for the reaction pathway including possible side reactions was presented. It involves first the hydrolysis of the amide and imine plus the loss of amine from the aminol, which is formed via hydrogen addition to the amide. Furthermore, transamidation of the starting substrate with the formed secondary amine gives an amide. All these steps liberate ammonia.

In 2012, Cole-Hamilton, Leitner, Klankermayer, and co-workers published an improved procedure for the hydrogenation of aliphatic amides due to reproducibility problems of the former protocol. Crucial for the success of this transformation is the quality of the Triphos^{Ph} ligand and a higher reaction temperature (200 and 220 °C).[13]

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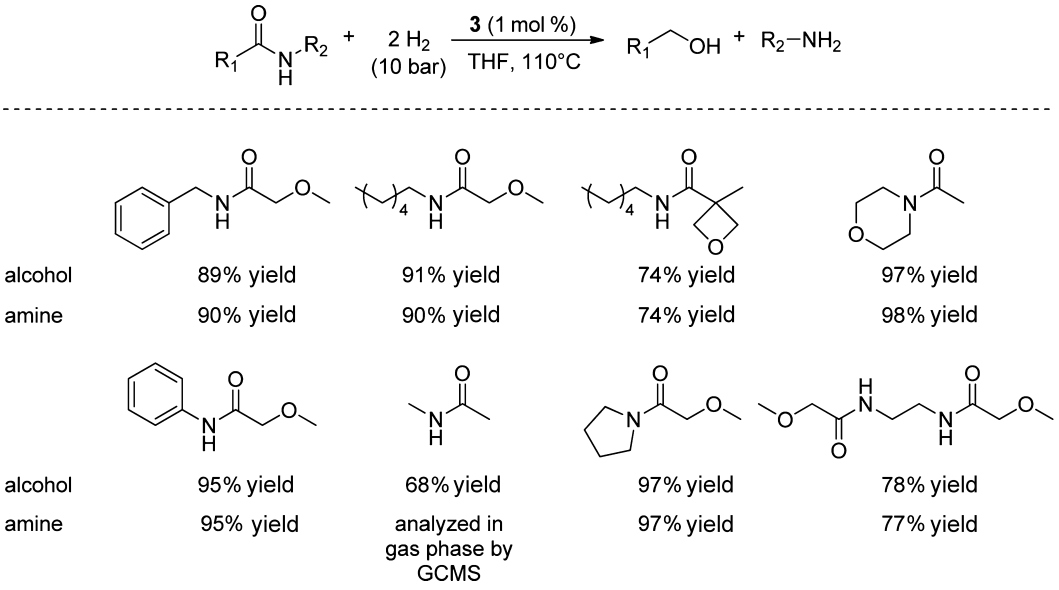
Scheme 3. Amide hydrogenation by Milstein et al. (selected substrates)



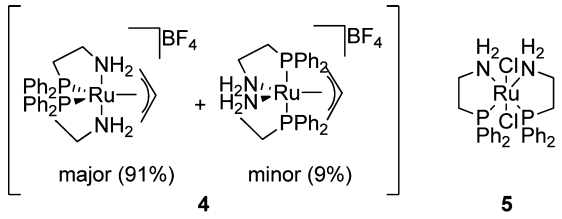
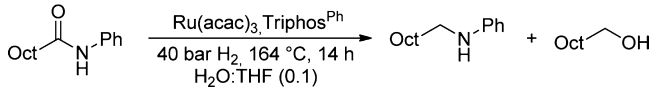


Figure 2. Complexes **4** and **5** used by Bergens and co-workers.

Most recently, interesting protocols for the methylation of amines using carbon dioxide and hydrogen were developed by the groups of Leitner and Klankermayer as well as our group.[14] It is noteworthy that, in this reaction sequence, most likely catalytic hydrogenation of in situ-generated formamides occurs. Combination of Ru(III) precursors, Triphos^{Ph}, and either acid additives or LiCl allows for the efficient synthesis of methylated amines in good to excellent yields (Scheme 6).

For the first time various functional groups are tolerated in homogeneous amide hydrogenations. Furthermore, a selective monomethylation of diamines and a convenient synthesis of ^{13}C-labeled drugs illustrate the synthetic utility of this novel method (Scheme 7).

Scheme 5. Ru/Triphos^{Ph}: *N*-Phenylnonamide reduction

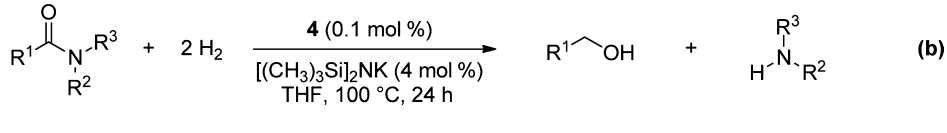


3. CATALYTIC REDUCTION OF ESTERS

The reduction of esters to alcohols is one of the fundamental redox transformations in organic chemistry. It is frequently used in natural product synthesis, for the preparation of organic building blocks and in industry for the production of pharmaceuticals, agrochemicals, flavors, and fragrances. Common methods for ester reduction make use of stoichiometric amounts of lithium aluminum hydride, dibutyl aluminum hydride, or boron hydride in organic solvents such as THF. Negative aspects of these procedures are the high costs, low

Scheme 4. Reaction conditions and selected substrate scope for the (a) lactam hydrogenation; (b) acyclic amide hydrogenation

R = Ph, n = 1: 100% yield
R = Me, n = 1: 5% yield
R = Ph, n = 2: 100% yield
R = H, n = 3: 23% yield



R^1 = Ph, R^2 = Ph, R^3 = Ph: 100% yield
R^1 = Ph, R^2 = Me, R^3 = Ph: 96% yield
R^1 = Ph, R^2 = H, R^3 = Ph: 50% yield
R^1 = Me, R^2 = Ph, R^3 = Ph: 100% yield
R^1 = Me, R^2 = Me, R^3 = Me: 50% yield
R^1 = Me, R^2 = H, R^3 = Ph: 70% yield

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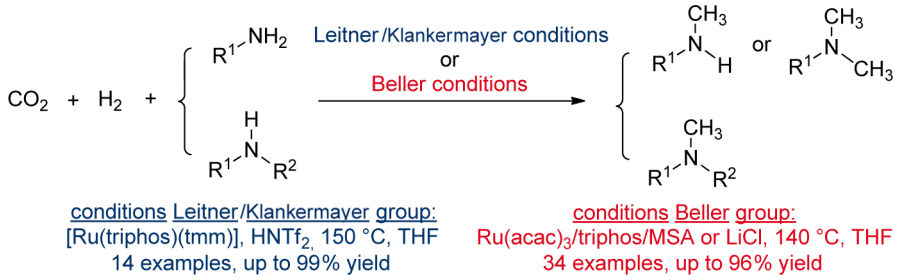
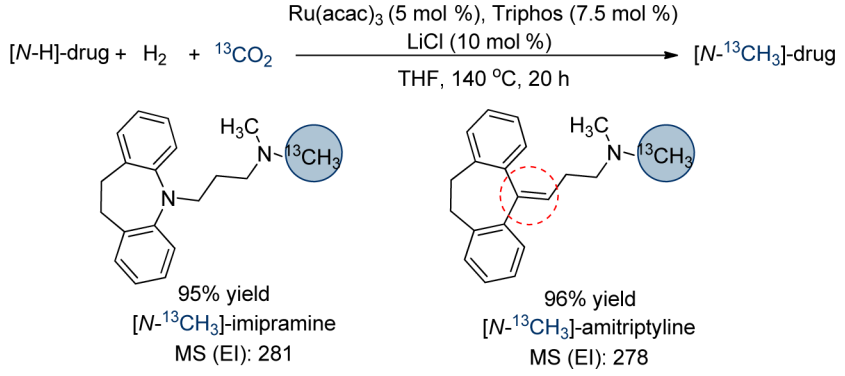
Scheme 6. Catalytic methylation of amines with carbon dioxide via hydrogenation of formamides



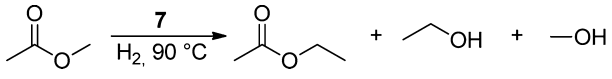
Scheme 7. Direct synthesis of [*N*-$^{13}CH_3$]-imipramine and amitriptyline from $^{13}CO_2$[14]



atom economy, laborious workup procedures, and safety.[15] Advantageously, in catalytic hydrogenations no side products are formed compared to the classic stoichiometric reduction processes. Hence, on larger scale heterogeneous metal oxide-based catalysts are applied to hydrogenate carboxylic acid esters, e.g. fatty acid esters, to the corresponding alcohols.[16,17] Unfortunately, catalytic hydrogenation in the presence of these catalysts needs high temperature and pressure. In order to perform homogeneous hydrogenation of esters under milder conditions, ruthenium, iridium, and osmium complexes have been explored and offer some potential.

3.1. Ruthenium. *3.1.1. The Start and the Triphos Age.* Early studies by Grey and Pez et al. describe a mild hydrogenation of unactivated carboxylic acid esters using the ruthenium hydride complexes $[(Ph_3P)Ph_2P(C_6H_4)\text{-}RuH_2^-K^+(Et_2O)\cdot C_{10}H_{18}]_2$ (**6**) and $[(Ph_3P)(Ph_2P)RuH_2^-K^+\cdot diglyme]_2$ (**7**).[18,19] More specifically, **7** hydrogenated methyl acetate to give ethanol, methanol, and ethyl acetate (transesterification product) in toluene solution (Scheme 8). It is noteworthy that the reaction without any solvent did not proceed. In addition, activated esters, e.g. methyl trifluoroacetate and trifluoroethyl trifluoroacetate were reduced. In the latter cases, complex **7** led to higher conversions than complex **6**.

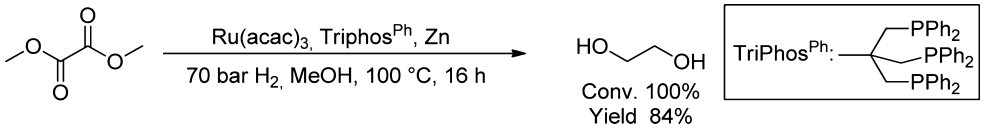
Scheme 8. Hydrogenation of methyl acetate



In the same year, Bianchi and Matteoli and co-workers applied the ruthenium carbonyl hydride complex $[Ru_4H_4(CO)_8(PnBu_3)_4]$ under forcing conditions for the reduction of dicarboxylic acid esters.[20] In 1986, Matteoli et al. presented the hydrogenation of dimethyl oxalate to methyl glycolate in the presence of related complexes $[Ru(CO)_2(CH_3COO)_2(PR_3)_2]$ (R = Bu, Ph). Under harsher conditions (180 °C, 130 bar H_2, 144 h) consecutive reduction to ethylene glycol took place. Nevertheless, di-isopropyl oxalate, di-*n*-propyl oxalate, and di-*n*-hexyl oxalate were transformed into the corresponding alkyl glycolates with conversions up to 100%.

After Hara and Wada disclosed in the early 1990s an appropriate catalytic system ($Ru(acac)_3$/tri-*n*-octylphosphine/*p*-TsOH, NH_4PF_6, phosphoric acid, or its derivatives) for the reduction of lactones and anhydrides,[21] Elsevier reinvestigated this system in 1997/1998 and developed a more active system for the ester hydrogenation consisting of $Ru(acac)_3$/Triphos^{Ph} and zinc as additive (Scheme 9).[22] With dimethyl oxalate as substrate they tested several phosphine ligands and obtained the following order of activity: Triphos^{Ph} ≫ $[CH_2P(Ph)\text{-}C_2H_4PPh_2]_2$ ≈ $P(C_6H_{11})_3$ > $PhP(C_2H_4PPh_2)_2$ > PPh_3 > $Ph_2PC_2H_4PPh_2$. A facial coordination of the ligand is essential for the high catalytic activity. The use of $Ru(acac)_3$/Triphos^{Ph} as catalytic system was expanded to the reduction of dicarboxylic acid esters as dimethyl phthalate and dimethyl

Scheme 9. Hydrogenation of dimethyl oxalate with Triphos^{Ph}



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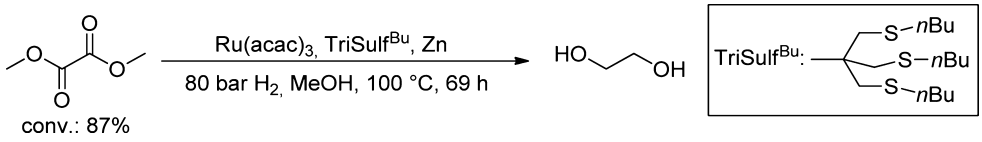
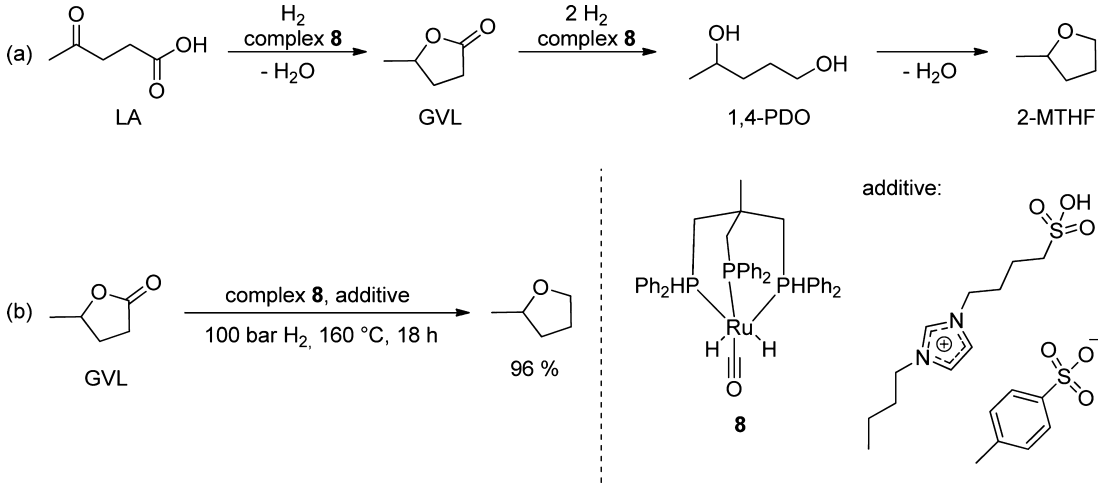
Scheme 10. Hydrogenation of dimethyl oxalate with TriSulf^{Bu}



Scheme 11. (a) Hydrogenation of levulinic acid with complex 8; (b) hydrogenation of GVL with complex 8 and additive



maleate, benzyl benzoate as well as methyl palmitate by replacing Zn with NEt_3.[23] It is noteworthy, that for benzyl benzoate the catalyst turnover number has been increased from 105 to 896 and >2000 by changing the solvent from isopropanol to fluorinated alcohols, e.g. 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexalfluoropropan-2-ol.

More recently, the same catalyst system (Ru/Triphos^{Ph}/Zn) was studied by Frediani et al. in 2010.[24] They described the hydrogenation of fumaric acid, succinic acid, and γ-butyrolactone to the corresponding diols in high yields and selectivities. Advantageously, in contrast to previous reports, no fluorinated solvents were necessary. As an extension, deuteration for the "one-pot" synthesis of isotopomeric 1,4-butandiol starting from fumaric acid has been accomplished.

The hydrogenation of methyl oxalate also proceeded successfully by substitution of the Triphos^{Ph} ligand by the sulfur analogue TriSulf^{Bu}.[25] To that time, this latter catalyst constituted a more active and selective system and represented the first example for ruthenium/sulfur ligand cooperation (Scheme 10).

Furthermore, Hanton et al. described in 2011 tripodal phosphine ligands *N*-Triphos^{Et} $N(CH_2PEt_2)_3$ and *N*-Triphos^{Ph} $N(CH_2PPh_2)_3$.[26] In combination with $Ru(acac)_3$ these ligands hydrogenated dimethyl oxalate. Unfortunately, lower rates in comparison to Triphos^{Ph} have been observed, perhaps due to decomposition of the labile *N*-Triphos scaffold during the catalytic reaction. Moreover, the authors tested new additives (e.g., zinc, water, silver iodide, and trimethylamine oxide) for the hydrogenation of dimethyl oxalate in the presence of $Ru(acac)_3$/Triphos^{Ph}, but the reaction rate could not be increased.

In the same year, Leitner and Klankermayer investigated the selective hydrogenation of biobased carboxylic acids.[27] Using the ruthenium/triphos complex **8** (Scheme 11) levulinic acid was reduced via γ-valerolactone (GVL, cyclic ester, 22% yield) and 1,4-pentanediol (1,4- PDO, 73% yield) towards the corresponding 2-methyltetrahydrofuran (2-MTHF, 3% yield). By addition of catalytic amounts of an ionic liquid as an acidic additive for the reduction of GVL, high selectivity and yield of 96% was achieved. A similar yield of 95% was observed by using the in situ catalyst system consisting of $Ru(acac)_3$ as precursor, triphos as ligand and the same additive.[27a]

The combination of different Ru precursors with the Triphos ligand gave rise to the first general homogeneous ester hydrogenation catalyst. Nevertheless, improvements of this catalyst system is still of major interest due to the disadvantages such as long reaction times, high pressures and limited functional group tolerance. Thus, the search for more active and defined hydrogenation catalysts continued.

3.1.2. Pincer-Type Catalysts. Milstein et al. published in 2006 the first homogeneous system for the hydrogenation of non-activated aromatic and aliphatic esters under relatively mild conditions without any additives, e.g. zinc, organic bases, inorganic acids, salts, or fluorinated alcoholic solvents, which constitutes an important progress.[28] The new ruthenium PNP complex **9** (2,6-bis-(di-*iso*-propylphosphino-methyl)pyridine) and the related PNN complex **1** (Figure 3) operate via an aromatization/dearomatization sequence. Importantly, the PNN ligand **1** showed in some cases better performance than the PNP ligand (**9**) which revealed less activity (Table 1).

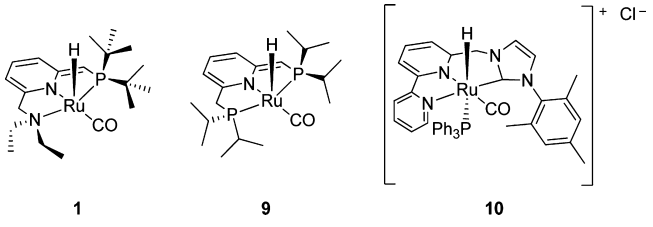


Figure 3. Ruthenium pincer complexes for hydrogenation of nonactivated esters by Milstein and co-workers.

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Table 1. Substrate Scope[a]

substrate	cat.	t [h]	T [°C]	conv. [%]	yield [%]
ethyl benzoate	**9**	16	115	7.5	benzyl alcohol (7), ethanol (7.5)[b]
ethyl benzoate	**9**	16	140	12	benzyl alcohol (11.5), ethanol (12)[b]
ethyl benzoate	**1**	4	115	99.2	benzyl alcohol (96), ethanol (99)[b]
methyl benzoate	**1**	4	115	100	benzyl alcohol (97), methanol (100)[b]
benzyl benzoate	**1**	7	115	98.5	benzyl alcohol (98)
hexyl hexanoate	**1**	5	115	82.2	1-hexanol (82.2)
ethyl butyrate	**1**	4	115	100	1-butanol (98), ethanol (98.6)
ethyl acetate	**1**	12	115	86	ethanol (85.6)
tert-butyl acetate	**1**	24	115	10.5	ethanol (10.5), *tert*-butanol (10.5)
dimethyl terephthalate	**1**	5	115	100	1,4-dimethanolbenzene (97), methanol (100)

[a]Catalyst **1** or **9** (1 mol %), 5.3 bar H_2, dioxane. [b]Traces of benzyl benzoate were formed.

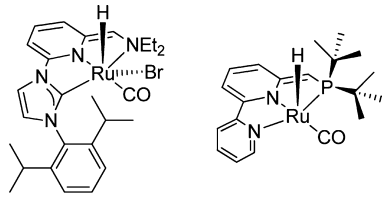
More recently, the PNN and PNP ligands were replaced by novel CNN-pincer complexes based on bipyridine-NHC (*N*-heterocyclic carbene) ligands in 2011 for hydrogenation of esters under milder conditions.[29] In the presence of catalytic amounts of base, complex **10** (Figure 3) allowed for the hydrogenation of several esters to the corresponding alcohols (Scheme 12). Notably, for the hydrogenation of nonactivated esters, complex **10** has been the most active system up to this time.

An excellent catalyst TON of 2840 was achieved with 50 bar H_2, 110 °C, 0.025 mol % **10**, and 0.025 mol % KO*t*Bu using ethyl benzoate as substrate within 12 h. Later on, the TON was increased by the group of Song.[30]

They developed a new pyridine-based CNN pincer ligand with NHC ligands and diethylamino arms and prepared the corresponding ruthenium complex **11** (Figure 4). A high efficiency for the reduction was obtained for several aromatic and aliphatic esters (yields ≥92%) within 2−3 h at 105 °C, 5.3 bar H_2, in the presence of complex **11** (1 or 2 mol %), KO*t*Bu (1 or 8 mol %) and toluene (2 mL).

Additionally, Milstein showed that complexes **10** (Figure 3) and **3** (Figure 4) were also effective catalysts for the hydrogenation of cyclic diersters to 1,2-diols.[31]

3.1.3. Complexes with Tri- and Tetradentate Ligands. In recent years, various Noyori-type catalysts have been investigated by Saudan,[11a] Kuriyama,[32] and Clarke[33] for the hydrogenation of carboxylic acid esters. Saudan et al. performed the reduction of methyl benzoate in the presence of 0.05 mol % ruthenium catalyst **12**−**17**, 5 mol % NaOMe, at 50 bar H_2, 100



11 **3**

Figure 4. Complex **11** by Song et al. and complex **3** by Milstein et al.

°C, for 1 h in THF as nonpolar solvent (Figure 5). The complexes **12**−**14** catalyze the reduction with excellent yields

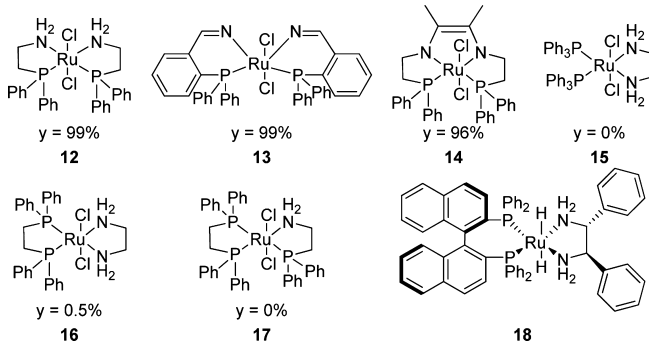


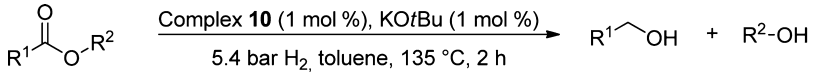
Figure 5. Hydrogenation of esters by Noyori-type catalysts.

between 96 and 99%, whereas complexes **15**−**17** led to either no or very low product yields. Because of their interest in flavors and fragrances, Saudan and co-workers demonstrated the selective hydrogenation of esters with a C−C double bond as well as efficient reduction of various aromatic, aliphatic, and cyclic esters. Notably, complex **12** has also been shown to be successful for hydrogenation of some lactones into diols. As an example, the synthesis of cetalox was presented, which is produced on large scale in the fragrance industry for its amber odor.[34]

In 2007, Bergens and his group performed ester and lactone hydrogenations with Noyori's ketone hydrogenation catalyst (Figure 5, complex **18**).[35] In addition to the demonstration of a small substrate scope, intermediates of the catalytic cycle were described. They found a high catalyst activity towards the hydrogenation of esters and lactones and showed that product formation inhibits the reaction at low temperature and pressure.

Complex **12** has also been used by Kuriyama and co-workers for hydrogenation of optically active esters under mild and neutral conditions.[32a] After a ligand screening, they discovered a new catalytic system by applying the chiral catalyst **19** to reduce several α- and β-substituted chiral esters to the corresponding alcohols (Scheme 13) without loss of the optical activity.

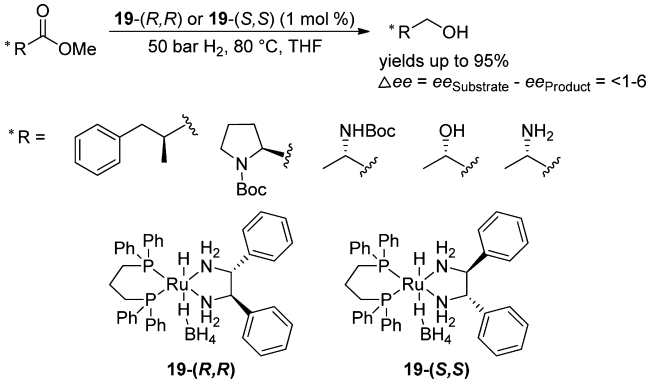
Scheme 12. Hydrogenation of esters catalyzed by complex 10



R^1, R^2: pentyl	1-pentanol 96%
R^1: butyl, R^2: ethyl	1-butanol 97%, ethanol 95%
R^1,R^2: benzyl	benzyl alcohol 89%
R^1: benzyl, R^2: ethyl	benzyl alcohol 97%, ethanol 94%

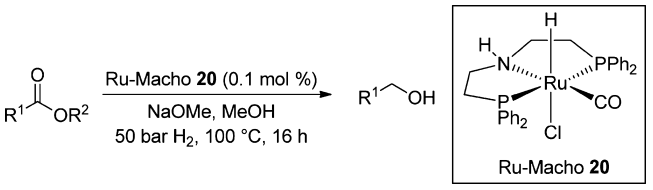
dx.doi.org/10.1021/op4003278 | *Org. Process Res. Dev.* 2014, 18, 289−302

Scheme 13. Hydrogenation of selected, optically active esters with [RuH(η^1-BH_4)(dppp)(dpen)] (19)



Lately, Kuriyama et al.[32b] described their recent investigations on the development of more active and efficient catalysts for industrial applications. They developed a new ruthenium complex (Ru-Macho **20**), which undergoes carbonylation and decarbonylation. Advantageously, the catalyst is not deactivated in MeOH, which is formed during the hydrogenation of methyl esters. Therefore, MeOH has been used as solvent to avoid separation problems. Aromatic, aliphatic substrates with *N*- and *O*-containing functional groups (in the α-position) and dimethyl esters have been reduced with high yields. Unfortunately, *N*- and *O*-containing functional groups in the β-position led to low yields, whereby isopropyl- and *tert*-butyl esters showed a good activity. A general reaction is presented in Scheme 14.

Scheme 14. Hydrogenation of various esters with complex 20



Besides, Kuriyama and co-workers investigated the challenging synthesis of industrially important (*R*)-1,2-propandiol, which constitutes a crucial intermediate for pharmaceuticals and 2-(l-menthoxy)ethanol as cooling agent (Scheme 15).

Clarke and co-workers performed the reduction of *p*-fluorobenzoic acid methyl ester by applying several in situ-formed ruthenium complexes **19**-(*S,S*) (Scheme 13) and **21**–**27** (Figure 6). For their substrate scope of aromatic and heteroaromatic esters catalyst **19**, **21** or **27** has been used to achieve very high isolated yields.[33]

In previous studies, Clarke et al. synthesized complex **22** for the first time and utilized this ruthenium catalyst for the reduction of an activated ester ($CF_3CF_2CF_2CO_2CH_3$). Here, an excellent yield of 100% was obtained. Unfortunately, dimethyl phthalate gave a mixture of isobenzofuran-1(3*H*)-one and 1,2-phenylenedimethanol (Scheme 16).[36]

In 2012, Gusev and co-workers focused on the development of new ruthenium catalysts for ester reduction.[37,38] Their catalysts showed excellent activity and efficiency with very high TONs up to 17000 while reducing few aliphatic and aromatic esters at low temperature (40–100 °C) and low catalyst loading (50 ppm [Ru]). Starting from ligands shown in Figure 7, a range of ruthenium and osmium complexes has been synthesized (Figure 8).

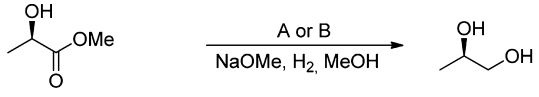
Besides, the dehydrogenative coupling of ethanol to ethyl acetate, they applied complex **34** for the hydrogenation of esters and imines.[37]

With the application of low catalyst loadings (0.005–0.025 mol %) of **34** at 50 bar H_2 and 40 °C and in the presence of 1–10 mol % of base, aromatic and aliphatic esters as well as a α-hydroxy and α-methoxy esters were reduced within 16–18 h in THF or neat to give the desired alcohols in high to excellent yields of 94–100%. In addition to the reduction of esters to alcohols, this system is also active for the dehydrogenative conversion of alcohols to esters.[38] Hence, complexes **37** and **38** were used for methyl benzoate reduction as well as for hydrogenation of aliphatic and cyclic esters and dimethyl carbonate. Additionally, methyl oleate was transformed to give in the presence of complex **38** a mixture of (*E*)- and (*Z*)-octadec-9-enols after 14 h. Worthy to note is the excellent TON (18000) obtained after 17 h for the hydrogenation of methyl benzoate. By applying complex **37** the back reaction was successfully performed for various alcohols such as ethanol, propanol, butanol, and heptanol.

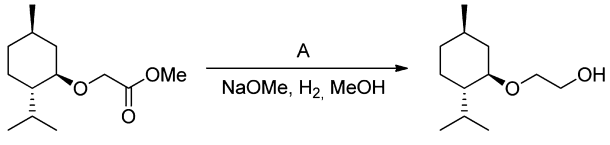
Recently, new complexes containing sulfur ligands instead of phosphorous have been synthesized by the same group.[39] With complexes **39**–**42**, esters were reduced more selectively towards the desired alcohol with high yields (85–100%) (Figure 9).

Especially the air-stable complex **39** proved to be more reactive for the hydrogenation of methyl benzoate and methyl

Scheme 15. Hydrogenation of (*R*)-1,2-propandiol and 2-(l-menthoxy)ethanol with complex 20



A: 10 mmol substrate, 0.01 mmol **20**, 40 °C, 50 bar H_2, 16 h: yield = 98%, $ee_{Substrate}$= 99.2, $ee_{Product}$= 98.6
B: 21,133 mol substrate, 10.6 mol % **20**, 26-28 °C, 40-42 bar H_2, 12 h: yield = 78%, $ee_{Substrate}$= 99.6, $ee_{Product}$= 99.2



A: 160 mmol substrate, 0.08 mmol **20**, 80 °C, 45 bar H_2, 5 h: yield = 87%

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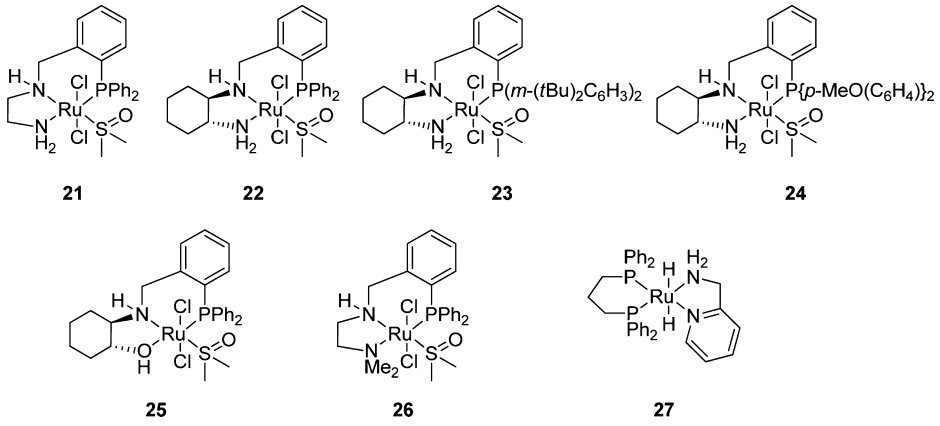
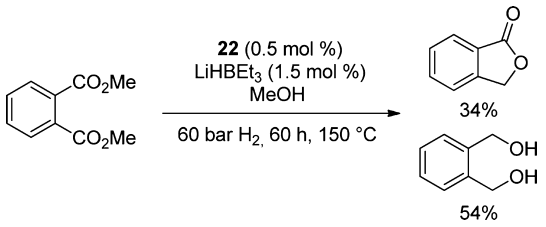


Figure 6. PP-, PNN-, and PNO-complexes **21**–**27**.

Scheme 16. Hydrogenation of dimethyl phthalate by Clarke et al.



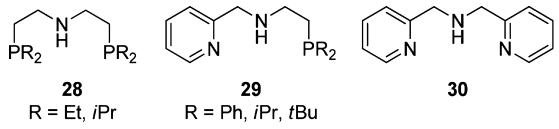


Figure 7. PNHP, NNHP, NNHN ligands for the synthesis of ruthenium and osmium complexes by Gusev et al.

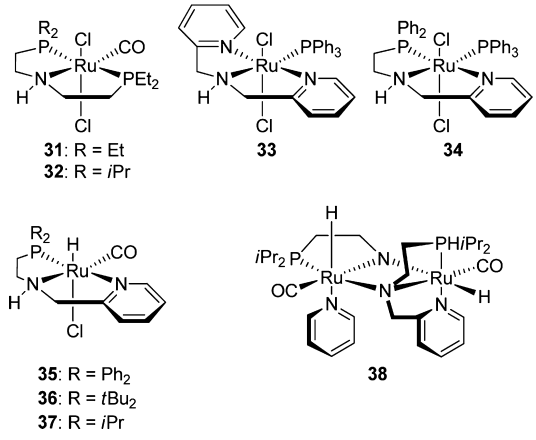


Figure 8. Ruthenium complexes **31**–**38** by Gusev et al.

hexanoate than complexes **12**, **20**, **34**, and **43**. As shown in Figure 10, various esters were reduced to give the

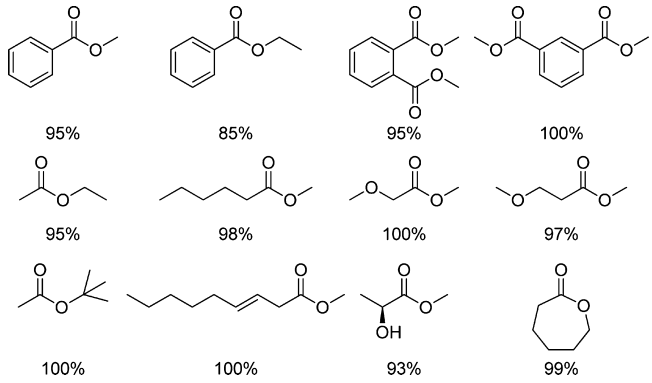


Figure 10. Conversions for ester reduction using complex **39**: substrate scope.

corresponding alcohols in high to excellent conversions. In the case of *(E)*-methyl non-3-enoate, the authors observed a product ratio of *trans*-3-nonen-1-ol:1-nonanol of 73:27.

These results revealed that Noyori-type catalysts can be replaced by complexes with less sensitive sulfurous ligands which prevent working with phosphines.

3.1.4. Miscellaneous Catalysts. Several other esters and lactones were hydrogenated with various Ru–phosphine and/or nitrogen ligand-containing systems as shown in Table 2.

3.2. Osmium. Interestingly, in 2012 Gusev and co-workers demonstrated the application of osmium-based catalysts for the hydrogenation of unsaturated esters. The most active catalyst was the osmium dimer **45** which successfully catalyzed the reduction of methyl 3-nonenoate, methyl oleate, and glyceryl trioleate to the corresponding alcohols with the retention of the C–C double bond. The back reaction (alcohol to ester) can be catalyzed as well (Scheme 17).[34,35]

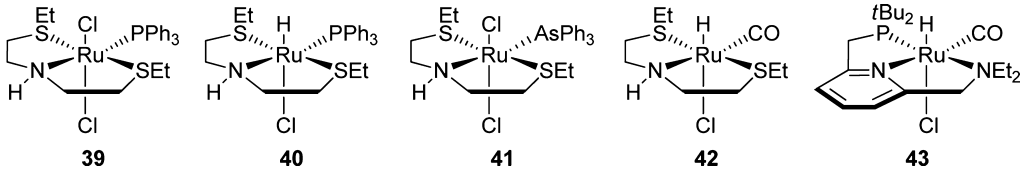


Figure 9. Ruthenium complexes **39**–**42** containing sulfur ligands by Gusev et al.

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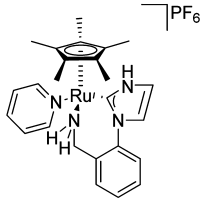
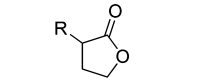
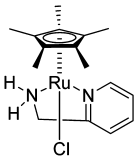
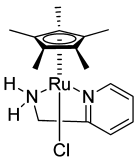
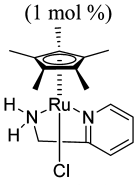
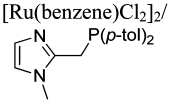
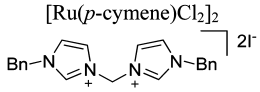
Table 2. Selected catalytic hydrogenations of carboxylic acid esters and analogues

Substrate	Catalyst (mol%)	Reaction conditions	Yield [%]	Reference
$PhCH_2CO_2CH_3$	$Ru(acac)_3/P(nC_8H_{17})_3$ (0.02 mol %/0.2 mol %)	10 bar H_2, 15 h, 200 °C, Zn (0.2 mol %)	4.4[a]	40
$PhCH_2CO_2CH_3$	 (0.07 mol %)	8 bar H_2, 3 h, 25 °C, KO*t*Bu (5.3 mol %)	23[b]	41
 R = C_6H_5, 4-$CF_3C_6H_4$, 4-$CH_3OC_6H_4$, $C_6H_5CH_2$, 4-$CH_3OC_6H_4CH_2$, 3-$C_6H_5CH_2OC_6H_4CH_2$, 3,4-$(OCH_2O)C_6H_3CH_2$	 (1 mol %)	50 bar H_2, 6-18 h, 100 °C, KO*t*Bu (25 mol %), isopropanol	74-90	42
 R = C_6H_5, 4-$CH_3OC_6H_4$	 (1 mol %)	50 bar H_2, 12-12.5 h, 100 °C, KO*t*Bu (25 mol %), isopropanol	81-87	42
	 (1 mol %)	50 bar H_2, 15 h, 100 °C, KO*t*Bu (25 mol %), isopropanol	81	42
R-CO_2CH_3	$[Ru(benzene)Cl_2]_2$/  (0.25 mol %/1 mol %)	50 bar H_2, 2-4.5 h, 100 °C, KO*t*Bu (10 mol %), THF	17-99	43a
R-CO_2CH_3	$[Ru(p\text{-cymene})Cl_2]_2$  (0.5 mol %/2 mol %)	50 bar H_2, 6 h, 100 °C, KO*t*Bu (30 mol %), 1,4-dioxane	32-92	43b

[a]Yield/TON. [b]Conversion.

Remarkably, the reduction of methyl oleate was successfully achieved after 4 h with almost full conversion, demonstrating the specific potential of this largely overseen class of hydrogenation catalysts.

4. CATALYTIC REDUCTION OF NITRILES

Amines represent major intermediates for the chemical industry as well as important natural products. Hence, their selective synthesis continues to attract the interest of chemists after many years. Applying imine or nitrile reductions with molecular hydrogen offers efficient and versatile strategies for selective C−N bond formation. In this respect, atom-economic catalytic hydrogenations represent a key technology for a "green" synthesis of amines. However, in comparison to the hydrogenation of imines, the reduction of nitriles has been less studied so far. A general problem for nitrile hydrogenation to primary amines (**A**) is the inevitable side reaction towards the secondary amine (**B**). Scheme 18 gives an overview of this unwanted side reaction.

4.1. Ruthenium. *4.1.1. Ruthenium Complexes.* Early studies describe the hydrogenation of nitriles with $Fe(CO)_5$ and $Ni(CO)_4$ at high temperature/pressure (~200 °C, ~140 bar H_2).[44] Later on, $Ru(PPh_3)_3Cl_2$ and Ru(CO)HCl were disclosed for this transformation in another industrial patent by Dewhirst. Here, the reduction proceeded already at milder conditions (130 °C with 40 bar H_2).[45] In 2000, Bianchini and Psaro performed the hydrogenation of benzonitrile. Besides the use of heterogenized catalysts $[(sulphos)Ru(NCMe)_3]$-$(OSO_2CF_3)/SiO_2$ (**46**), some homogeneous reductions with $[(sulphos)Ru(NCMe)_3](OSO_2CF_3)$ (**47**) (sulphos = ^-O_3S-$(C_6H_4)CH_2C$ $(CH_2PPh_2)_3$) were accomplished.[46] In THF as solvent, at 100 °C and using **47**, the secondary imine (*E*)-*N*-benzylidene aniline was obtained as the major product with a good yield of 65%. Unfortunately, the primary amine was obtained only in a low yield of 34%.When the temperature was

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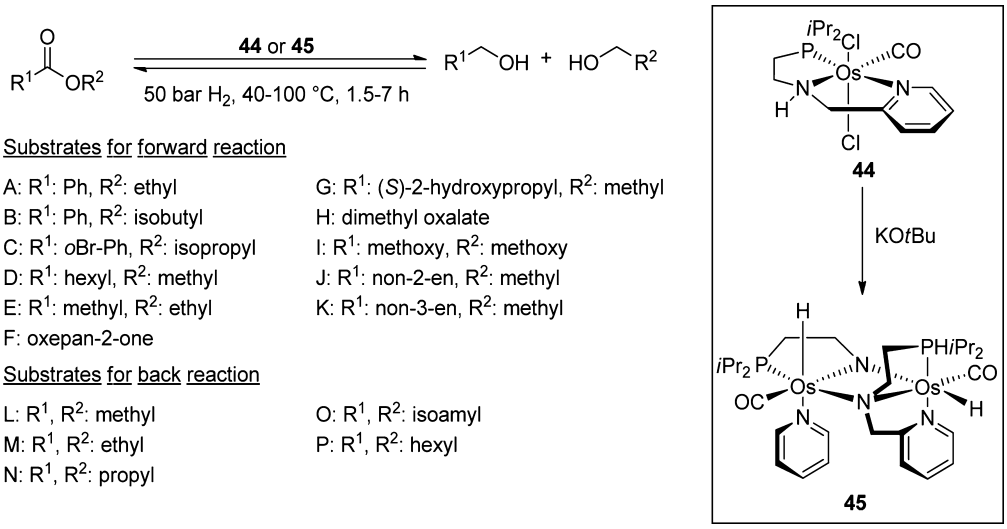
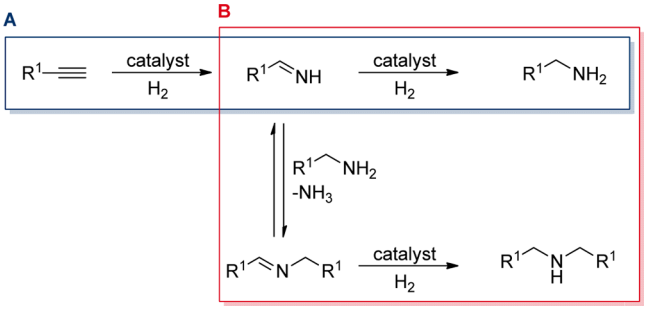
Scheme 17. Osmium-containing complexes 44 and 45 for the (de)hydrogenation reactions: Forward and back reaction



Scheme 18. Hydrogenation of nitriles and possible side reaction



decreased to 70 °C, the catalyst system seemed to be more selective, whilst giving only the secondary imine in excellent yield (98%) after 1.5 h.

Two years later, an improvement was reported by the group of Hidai who synthesized new ruthenium complexes **48** containing bis(diarylamido)/thioether ligands (Figure 11), which catalyzed the hydrogenation of benzonitrile when treated with PCy_3.[47]

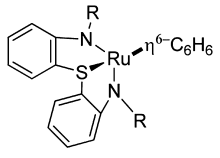
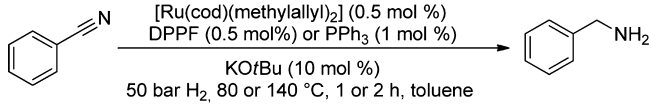


Figure 11. Ru complexes from Hidai and co-workers for hydrogenation of benzonitrile.

The highest selectivity (94%) and yield of 92% for benzyl amine was achieved with additional base (NaO*t*Bu), at 30 bar H_2, 80 °C after 18 h. Additionally, they noticed that the product distribution was affected by the substituent on the amide ligand.

Further progress has been achieved by our group. Using benzonitrile as model substrate, two appropriate catalyst systems have been developed (Scheme 19) applying $[Ru(cod)(methylallyl)]_2$ as precursor and DPPF[48a] (1,2-bis(diphenylphosphino)ferrocene) or PPh_3[48b] (triphenylphosphine) as ligand.

Scheme 19. Ruthenium-catalyzed hydrogenation of nitriles by Beller and co-workers



To demonstrate the general applicability of these optimized systems, a broad variety of substrates was investigated under optimized conditions. To our delight, smooth hydrogenation was demonstrated with both catalyst systems for various aromatic nitriles with electron-donating and electron-withdrawing groups (e.g., methoxy, amino, ester, bromide, chloride, trifluoromethyl) in *ortho*- and *para*-positions. In addition, heteroaromatic substrates as well as alkyl nitriles were reduced in good yields. Moreover, our group performed selective hydrogenation of benzonitrile and derivatives by applying a combination of the ruthenium precursor in the presence of carbene ligands and additional base (Scheme 20).[49] This latter procedure constitutes the first example of Ru/carbene-catalyzed chemoselective reductions of C−N triple bonds.

4.1.2. Ruthenium−Hydride Complexes. In the beginning of the 1980s, Pez and Grey applied ruthenium hydride complexes $[(Ph_3P)Ph_2P(C_6H_4)RuH_2^-K^+(Et_2O)\cdot C_{10}H_{18}]_2$ (**6**) and $[(Ph_3P)(Ph_2P)RuH_2^-K^+\cdot diglyme]_2$ (**7**)[19] in addition to the ester hydrogenation (section 3.1.1) for the reduction of acetonitrile, stearonitrile, trimethylacetonitrile, and benzonitrile. Notably, the addition of 18-crown-6 as additive was effective to obtain high conversion and to suppress the unwanted reaction pathway **B** as shown in Scheme 18.

The industrial interest in nitrile hydrogenation is shown by the work of Beatty and Paciello who patented this transformation using 0.1 mol % of $[RuH_2(H_2)_2(PCy_3)_2]$ (**50**) at 50−70 bar H_2 and a temperature between 80 and 100 °C.[50]

The catalytic activity of related complexes $RuH_2(CO)_2(PnBu_3)_2$ (**51**), $RuH_2(CO)_2(PPh_3)_2$ (**52**), and $RuH_2(PPh_3)_3$ (**53**) was described by Frediani et al. for the hydrogenation of nitriles.[51] Using benzonitrile as a benchmark system, all these catalysts allowed only for moderate conversion

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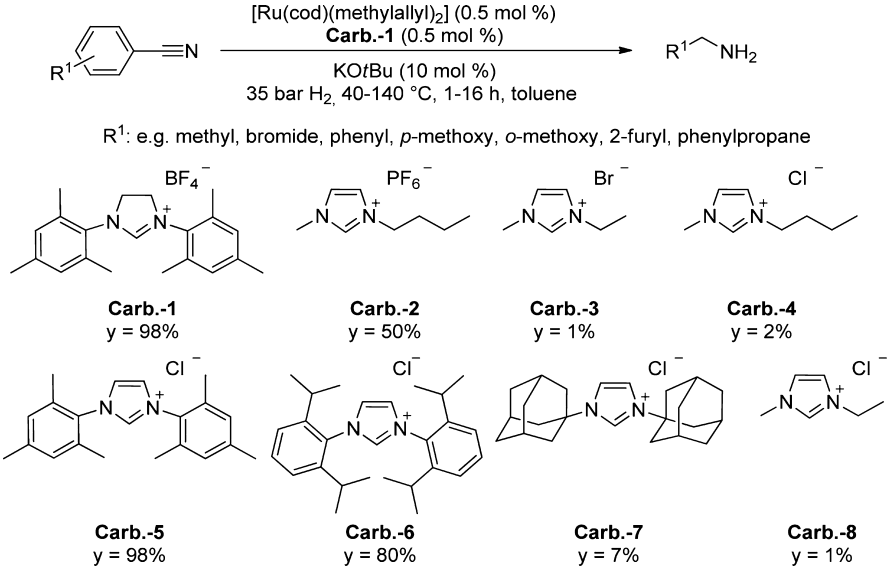
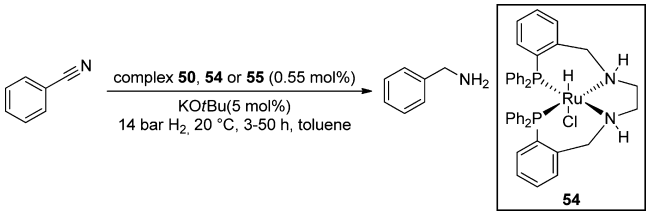
Scheme 20. Ruthenium-catalyzed hydrogenation of nitriles by applying Ru/carbene complexes



(highest conversion: 77% by using catalyst **52**). More specifically, all three catalysts did not form the primary amine as main product, instead *N*,*N*-dibenzyl amine was formed in moderate yields.

Treating $RuHCl(PPh_3)_3$ with $[PPh_2((o\text{-}C_6H_4)CH_2NHCH_2\text{-})]_2$ in THF led to isomeric *trans*-$RuHCl\{ethP_2(NH)_2\}$ (**54**). After activation of **54** with KO*t*Bu as base, benzonitrile was reduced to benzyl amine with good activity (Scheme 21).[52] Apart from the latter catalyst, $RuHCl\{tmeP_2(NH)_2\}$ (**55**) was also active similar to the combination of **54**+**50** and **55**+**50**.

Scheme 21. Hydrogenation of benzonitrile with complexes 50, 54 and 55



The addition of KH as base to the reaction mixture using complex **54** led to a shorter reaction time of 3 h since traces of water were removed. Consequently, the reductions proceed more rapidly and selectively.

More insight into the mechanism of nitrile hydrogenations using complex **56** was given by Grellier and Sabo-Etienne et al. in 2010.[53] Surprisingly, the authors demonstrated that this precatalyst is converted with one (**A**) or two (**B**) equivalents of benzonitrile to give the corresponding cyclometalated imine complexes **57** and **58** as the resting state of the catalyst (Scheme 22).

It is assumed that key to success for this reaction is the *ortho*-directed C−H activation of the aryl group. All the complexes **56**−**58** were successfully used for the hydrogenation of benzonitrile to benzyl amine under mild conditions. As shown in Table 3, almost no difference in the catalyst activity is observed.

Another ruthenium hydride complex with pincer ligands was described for nitrile reduction in 2011 by the group of

Scheme 22. Hydrogenation of benzonitrile with complex 56

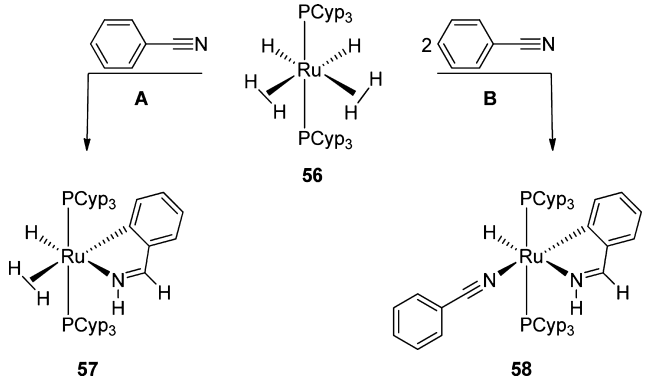


Table 3. Hydrogenation of benzonitrile towards benzyl amine (I) and dibenzyl imine (II)[a]

		conversion of benzonitrile (%)		product ratio of I:II (%)	
catalyst	solvent	2 h	24 h	2 h	24 h
56	pentane	94	94	94:6	94:6
56	THF	56	96	96:4	99:1
56[b]	THF	62	98	22:77	96:4
56	none	84	97	0.1:99.9	89:11
57	THF	68	97	96:4	99:1
58	THF	68	96	98:2	99:1

[a]Catalyst **56**, **57** or **58** (0.5 mol %), 22 °C, 3 bar H_2, THF. [b]0.2 mol % catalyst.

Leitner.[54] Under optimized conditions, aromatic and aliphatic nitriles were hydrogenated with complex **59**. However, relatively high pressure, high temperature, and long reaction times were necessary to obtain yields between 36 and 96%.

Remarkably, adding a small amount of water (5 equiv relative to the catalyst) provided increased conversions and selectivities towards primary amines (Scheme 23).

4.2. Rhodium. Rhodium(I) hydrides were first disclosed in 1979 by Yoshida, Okano, and Otsuka for the catalytic hydrogenation of several nitriles.[55] In more detail, $RhH(PiPr_3)_3$ (**60**) and $Rh_2H_2(\mu\text{-}N_2\{P(cyclohexyl)_3\}_4$ (**61**) proved to

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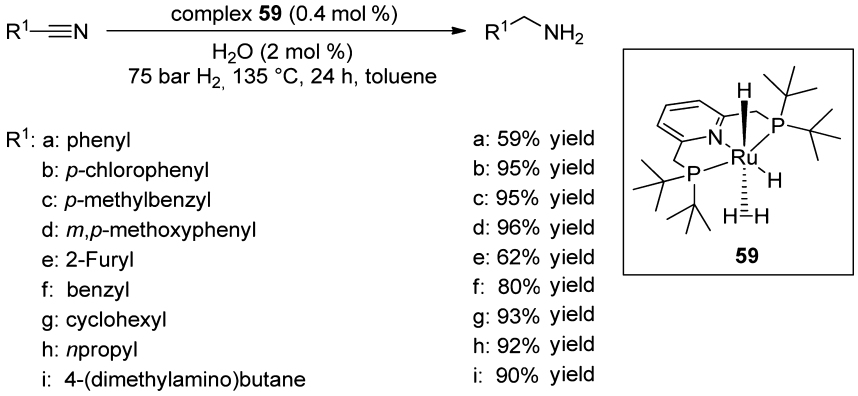
Scheme 23. Hydrogenation of nitriles with the nonclassical ruthenium hydride pincer complex 59



hydrogenate aromatic and aliphatic nitriles to give the corresponding primary amines with very high yields up to >99%.

Later on, complex **60** was also used by Eckert et al. for the hydrogenation of phenylacetonitrile and benzonitrile in THF and CO_2-expanded THF (20 bar) at room temperature with molecular hydrogen.[56] As shown in Table 4, in two cases the yield of the primary amine was increased by the addition of CO_2. The authors explained this fact with the in situ preparation of the primary amine from the in-solution remaining metal center. It should be noted that the product as carbamic acid or ammonium carbamate can be easily separated from the homogeneous catalyst.

Table 4. Rh-catalyzed hydrogenation of benzonitrile and phenylacetonitrile in THF and CO_2-expanded THF[a]

substrate	CO_2 pressure [bar]	yield [%][b]
benzonitrile	0	47
benzonitrile	20	61
phenylacetonitrile	0	95
phenylacetonitrile	20	96

[a]Catalyst **60** (20 bar H_2, 23−25 °C, 20 h, THF). [b]Yield is calculated from the total amount of the primary amine derivatives in the solution and precipitation.

4.3. Iridium. In 1992, Chin and Lee described the first iridium-catalyzed hydrogenation of aromatic and aliphatic nitriles. Unfortunately, a mixture of products was observed.[57] $[Ir(cod)(PPh_3)(PhCN)_2]ClO_4$ (**62**), $[Ir(cod)(PPh_3)_2]ClO_4$ (**63**), and $[Ir(cod)(PhCN)_2]ClO_4$ (**64**) have been deployed in different solvents, e.g., dichloromethane, methanol, and benzol. Hydrogenation of the nitrile in dichloromethane proceeded best (except catalyst **63**) compared to other polar- and nonpolar solvents. Furthermore, during catalysis with complex **64** metallic iridium powders are generated in combination with molecular hydrogen. Therefore, iridium metal and probably nanoparticles are formed, which are responsible for the hydrogenation of the phenyl ring of benzonitrile.

5. CONCLUSION AND OUTLOOK

On the basis of pioneering work in the 1960s−1970s, it has been demonstrated in the last two decades that different noble metal complexes allow for the hydrogenation of aromatic and aliphatic carboxylic acid derivatives to the corresponding alcohols and amines. Nowadays even chemoselective hydrogenations of such functional groups are possible in the presence of unsaturated compounds. Typically, these hydrogenations are performed using Ru complexes in combination with multidentate ligands. Clearly, the reported homogeneous reactions are still far off from immediate industrial applications, and also the substrate scope should be further improved. Hence, more mechanistic work needs to be performed because this constitutes the basis for further progress of molecular-defined catalysts. A detailed understanding of the elementary steps and the relationships between structure and action will lead to enhanced catalyst activity and productivity which are crucial issues with respect to practical applications.

What do we expect for the future in this area? With respect to methodology development, catalytic hydrogenations of amides to amines should work in a more general manner, applying milder conditions. Clearly, a "dream reaction" in the area of hydrogenation of carboxylic acid derivatives would be the selective hydrogenation of esters to ethers. So far, no examples exist for this valuable reaction. Regarding catalyst improvements it is highly desirable to establish also non-noble metal systems for these transformations. The advantages of biomimetic or bioinspired non-noble metal complexes in catalysis are obvious. Here, we think especially iron, copper, and nickel complexes will offer valuable opportunities.

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Notes

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Biographies

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Kathrin Junge, born in 1967 in northern Germany, received her PhD degree in chemistry from the University of Rostock in 1997 working with Prof. E. Popowski. After a postdoctoral position in the Max-Planck group of Uwe Rosenthal, she joined the group of Matthias Beller in 2000. Since 2008, she is group leader for homogeneous redox catalysis at LIKAT. Her scientific work has been published in >100 publications. She has been involved for years in catalysis research, where she has developed efficient catalytic hydrogenations for ketoesters and for other carbonyl compounds including carboxylic acid derivatives. Moreover, several new ligands especially for hydrogenation reactions were established by her. Her current main interest is the development of environmentally benign and efficient catalytic reactions based on cheap, nonprecious metals.

Matthias Beller, born 1962 in Gudensberg, Germany, studied chemistry at the University of Göttingen, Germany, where he completed his PhD thesis in 1989 in the group of L.-F. Tietze. As recipient of a Liebig scholarship, he then spent one year with K. B. Sharpless at Massachusetts Institute of Technology, United States. From 1991 to 1995, Beller worked in industry. Then, he moved to the Technical University of München as Professor for Inorganic Chemistry. In 1998, he relocated to Rostock to head the Institute for Organic Catalysis, which became in 2006 the Leibniz-Institute for Catalysis. The work of his group was published in >600 original publications and reviews, and >90 patent applications have been filed in the past decade. He has received several awards including the Otto-Roelen Medal and the Leibniz-Price of the DFG. In 2006, he was also awarded "Entrepreneur of the Year" of Rostock and he received the German Federal Cross of Merit. He received the first "European Prize for Sustainable Chemistry", the "Paul-Rylander Award" of the Organic Reaction Catalysis Society of the United States. and the Gay-Lussac-Alexander-von-Humboldt-Prize of the French Academy of Sciences. Matthias Beller is head of the German Chemical Society working group "Sustainable Chemistry" and a member of three German Academies of Sciences including the German National Academia "Leopoldina". He is married to Dr. Anja Fischer-Beller and they have two sons.

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